

# 2011 Military Health System Conference

## Advances in Translational Medical Research

*The Quadruple Aim: Working Together, Achieving Success*

CAPT Melissa Kaime, M.D., FACP

January 25, 2011



Congressionally Directed Medical Research Programs

*The views expressed in this presentation are those of the author and may not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.*

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# Mission and Vision



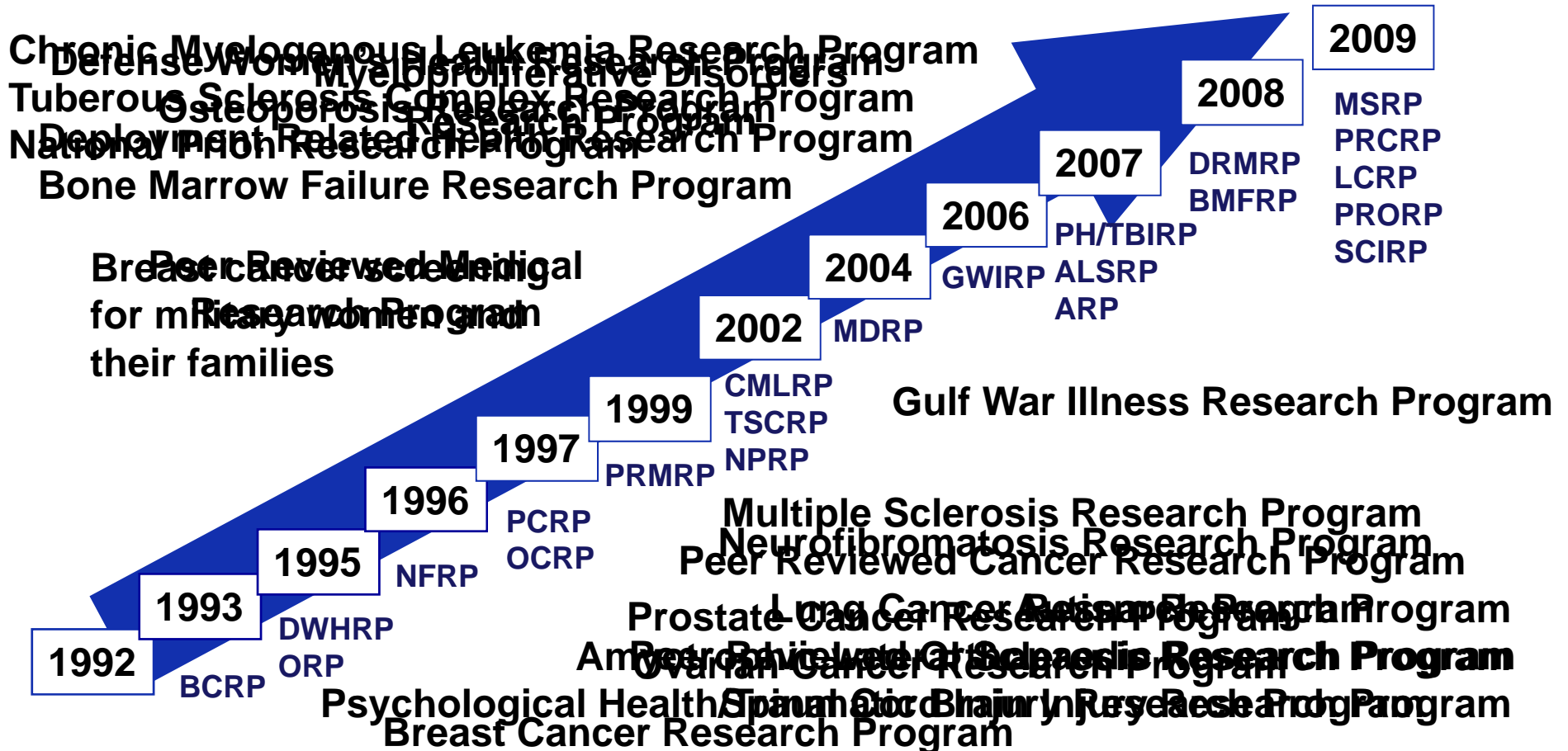
## Mission

We provide hope by promoting innovative research, recognizing untapped opportunities, creating partnerships, and guarding the public trust.

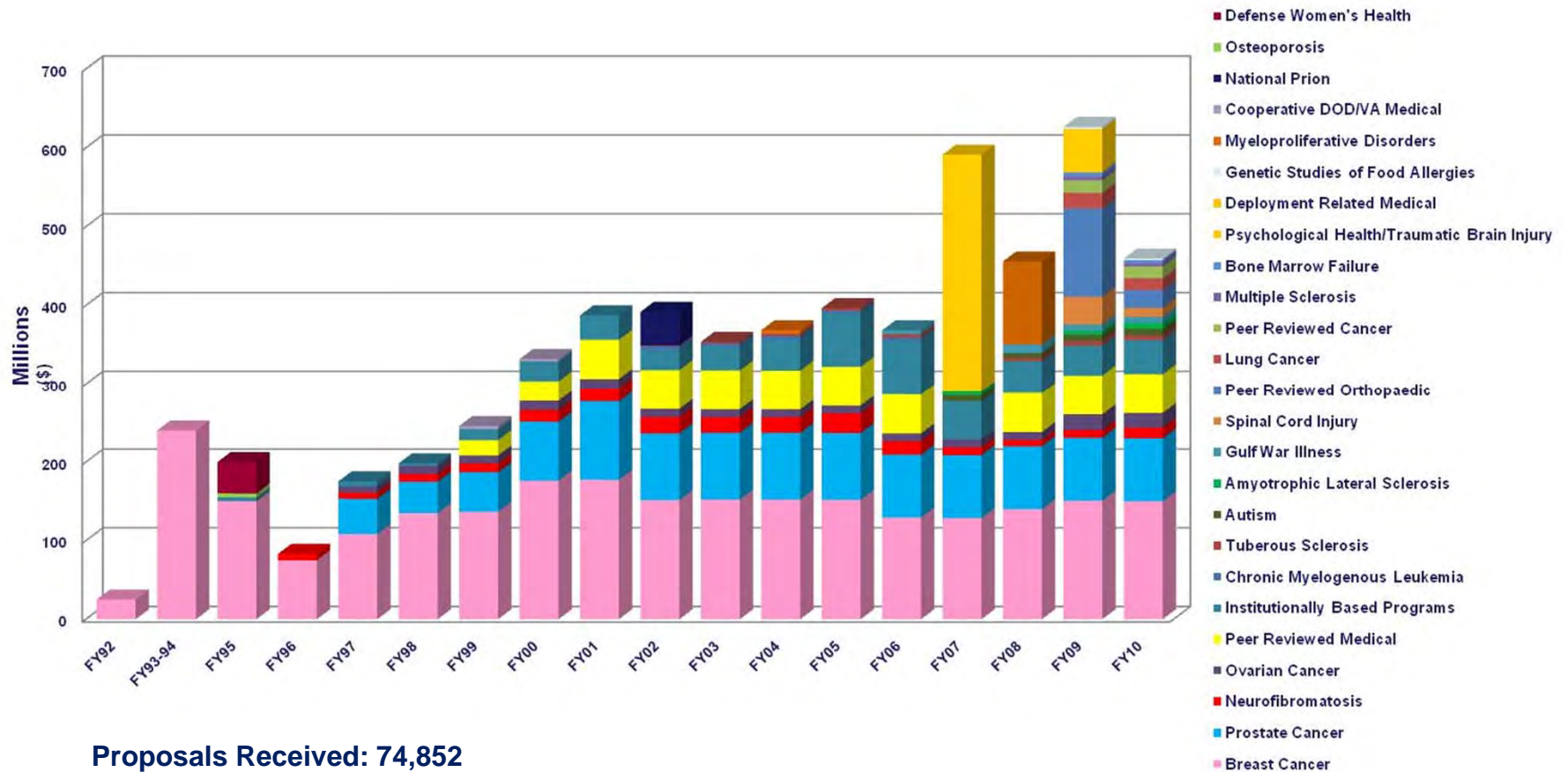
## Vision

Find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public.

# Program History



# Scope of CDMRP Funds and Awards



**Proposals Received: 74,852**  
**Grants Funded: 10,409**  
*As of 12-17-2010*

# CDMRP Unique Features



- Disease-specific research funds added to DoD budget by Congress
- Vision is adapted yearly, and award mechanisms are changed as needed
- Two-tier formal review of proposals – Institute of Medicine model
- Consumer advocates involved throughout process
- Fund highly innovative research
- Unique peer review:
  - No standing panels
  - No contact between reviewers and applicants
- Funding flexibility
  - No “pay line;” funding recommendations based on portfolio balance, relative innovation, and impact
  - Funds obligated up front; no out-year budget commitments
  - No continuation funding



# CDMRP Partnerships



## Advocates

- ◆ Demonstrate need
- ◆ Participate at all levels
- ◆ Passion and perspective



## Congress

- ◆ Add funds to budget
- ◆ Targeted guidance
- ◆ Opportunity to leverage



**IMPROVE  
HEALTH  
(CURE)**

## Researchers

- ◆ Innovation and gaps
- ◆ Risk/Benefit
- ◆ Product-oriented

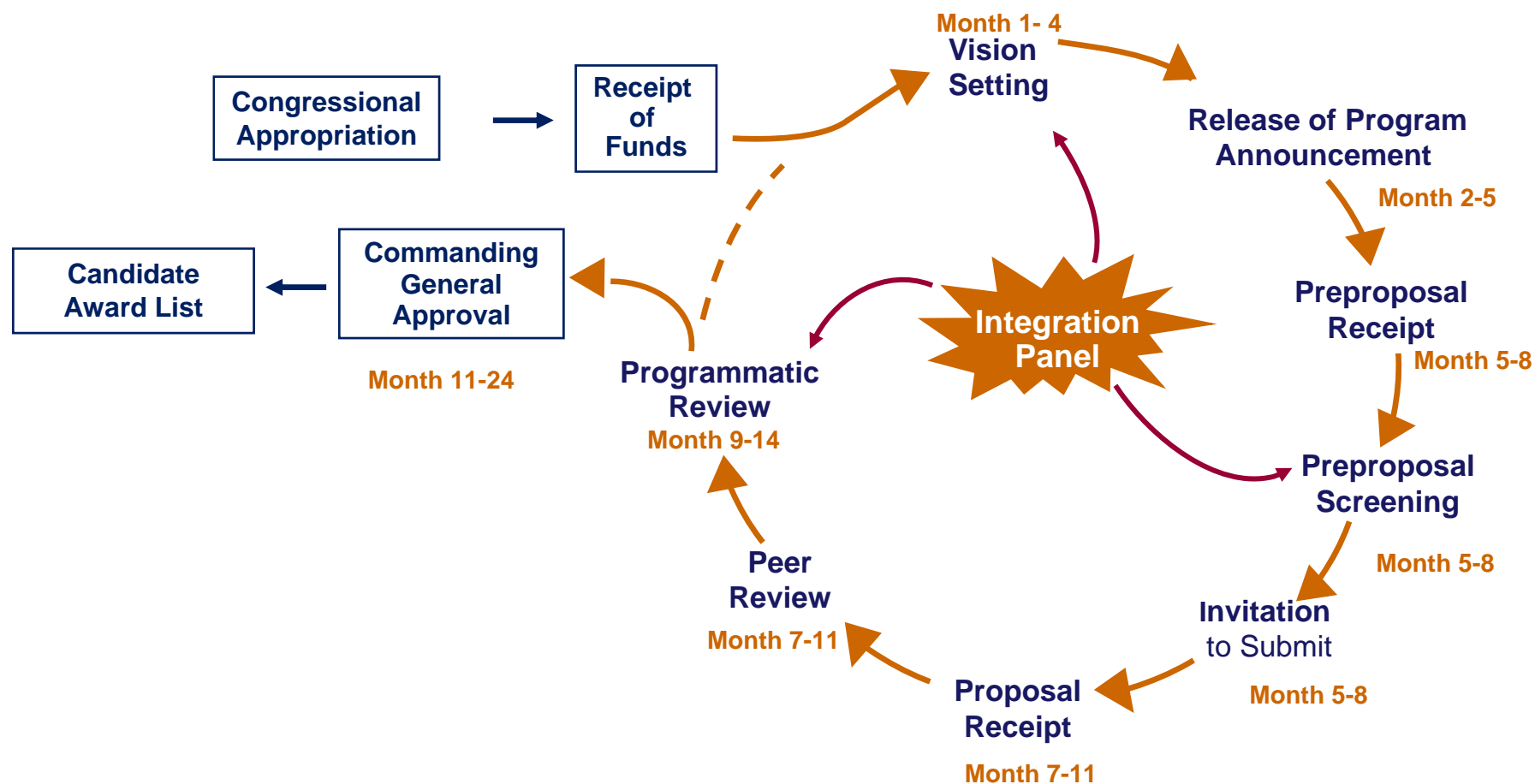


## DoD

- ◆ Program management
- ◆ Regulatory and budget requirements
- ◆ Institute Of Medicine model



# CDMRP Program Cycle



# Innovative Two-Tier Review Process



**Goal:** To **find** scientifically meritorious and innovative proposals, and **fund** those that best fulfill program goals



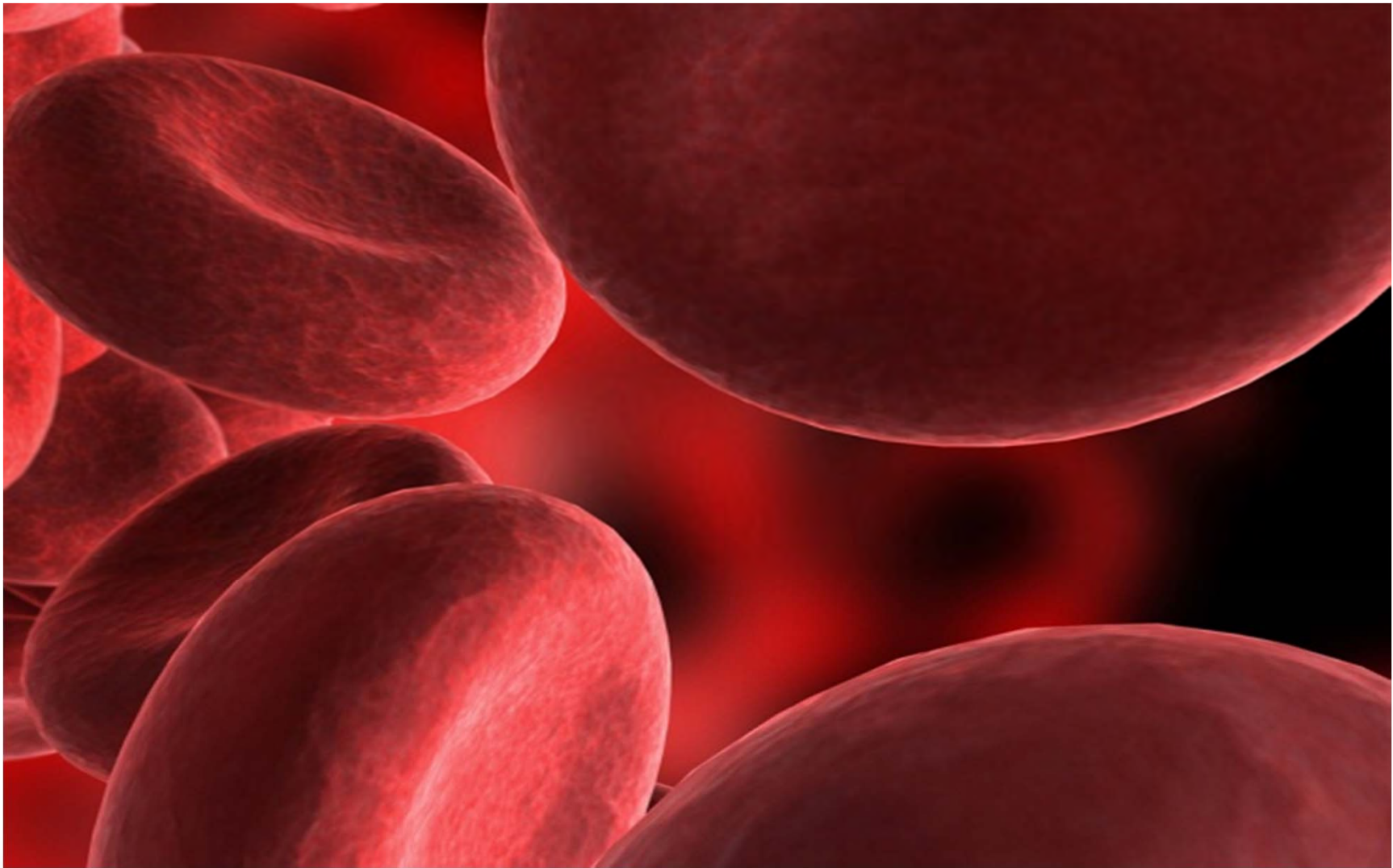
- Peer Review
  - Evaluation of scientific merit
  - Criteria-based evaluation
  - Proposals evaluated within related disciplines
- Products:
  - Proposal scoring
  - Summary statements
- Programmatic Review
  - Evaluation of programmatic relevance
  - Comparison-based evaluation
  - Proposals evaluated across multiple disciplines
- Product:
  - List of funding recommendations for the Commanding General, USAMRMC

# What Does the CDMRP Fund?



- Innovative, high-risk/high-gain research that can leapfrog advancements
- New collaborations and partnerships
- Research to improve patient/survivor quality of life
- Future innovators and leaders in the field
- Research to answer current needs
- Research to define and reduce health disparities

# High-Risk/High-Gain Research



# High Risk/High Gain: Herceptin



## FY93 BCRP Investigator-Initiated Research Award Dr. Dennis Slamon, UCLA

- Examined the mechanism of action of Herceptin, a humanized monoclonal antibody, against the *Her2/neu* receptor
- Herceptin is the first humanized antibody approved for treatment of Her2-positive metastatic breast cancer (Genentech; 1998)
- Herceptin is now standard of care for the adjuvant treatment of early-stage Her2-positive breast cancer
- Phase II clinical trials are in progress for non-small lung cancer, acute lymphoblastic leukemia, and ovarian cancer



*Dr. Slamon's research efforts led to the making of a Lifetime Television movie, "Living Proof"*

# Collaborations and Partnerships



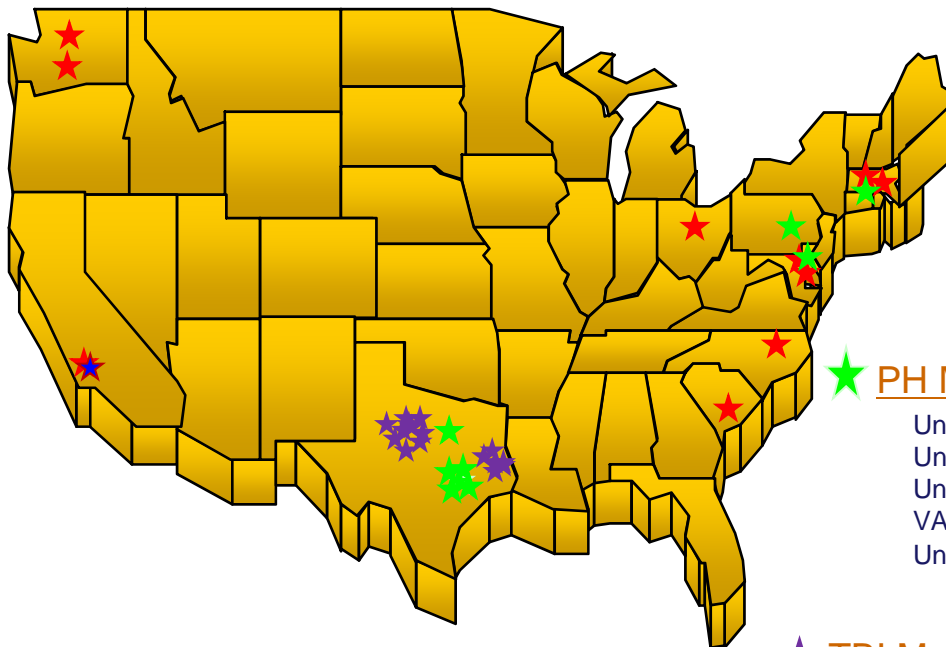
# CDMRP PH and TBI Consortia



## PH/TBI Clinical Consortium: Injury & TRAumatic STress Consortium (INTRuST)

★ Clinical Consortium Coordinating Center  
University of California, San Diego

★ Clinical Consortium Study Sites  
University of Maryland, Baltimore  
Uniformed Services University of the Health Sciences  
Spaulding Rehabilitation Hospital  
Dartmouth College  
University of Washington  
University of Cincinnati  
Duke University  
University of California, San Diego  
Medical University of South Carolina  
Madigan Army Medical Center



## ★ PH Multidisciplinary Research Consortia (STRONG STAR)

University of Texas Health Science Center at San Antonio  
University of Pennsylvania  
University of Texas at Arlington  
VA Boston Healthcare System  
Uniformed Services University of the Health Sciences

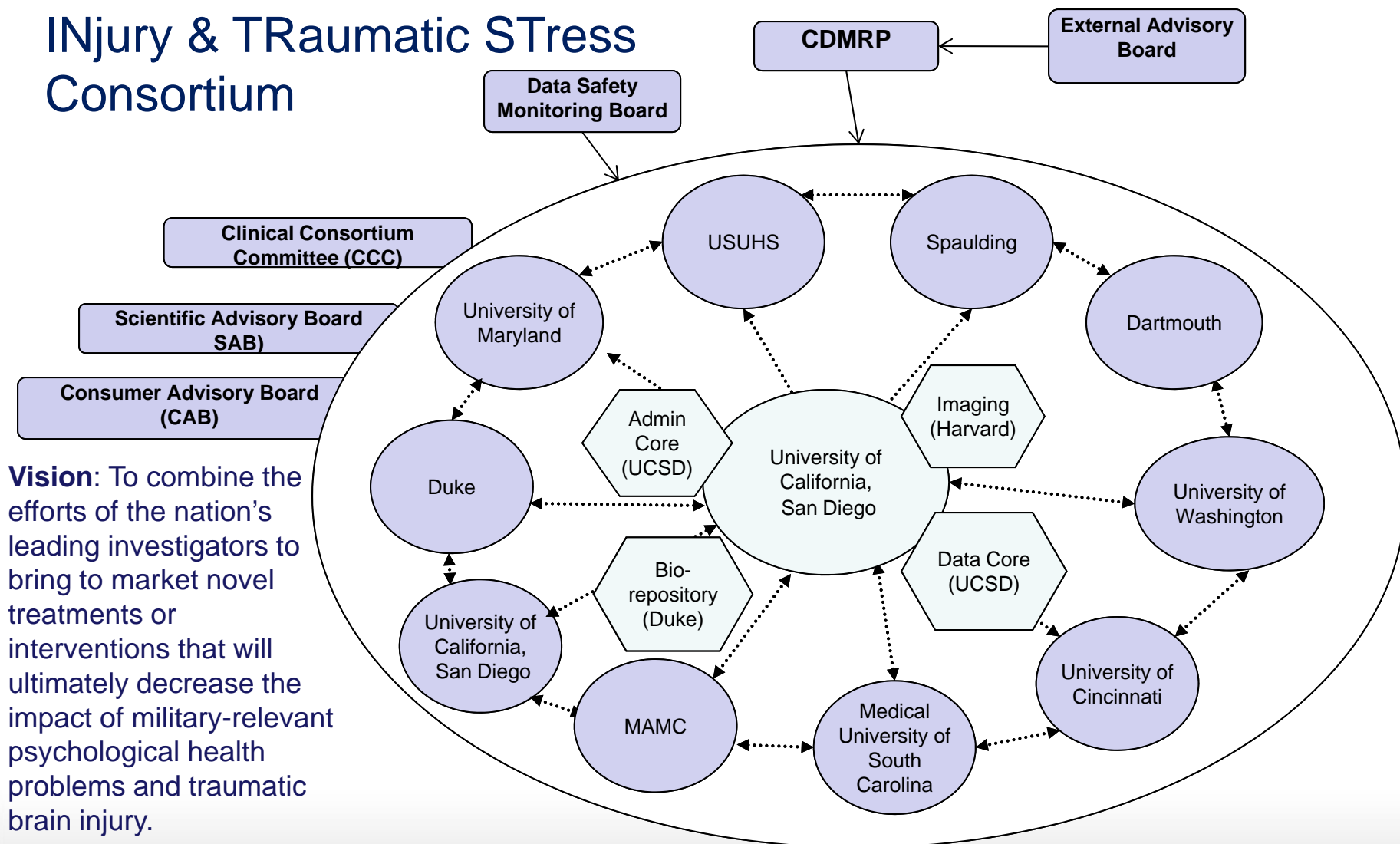
## ★ TBI Multidisciplinary Research Consortia

University of Texas Health Science Center at Houston  
Baylor College of Medicine  
Rice University  
University of Galveston  
Transitional Learning Center at Galveston

# Partnerships: INTRuST



## Injury & TRaumatic STress Consortium



**Vision:** To combine the efforts of the nation's leading investigators to bring to market novel treatments or interventions that will ultimately decrease the impact of military-relevant psychological health problems and traumatic brain injury.

2011 MHS Conference

# INTRuST Studies



## Main Studies

- Proof-of-Concept Trial of Ganaxolone in PTSD
- Effects of Telephone Follow-up on Outcome for Service Members with mTBI/PTSD
- Randomized Clinical Trial of Glyburide for TBI
- Initial Randomized Controlled Trial of ACT for Distress and Impairment in OEF/OIF Veterans
- Randomized Controlled Trial of Galantamine, Methylphenidate, and Placebo for the Treatment of Cognitive Symptoms in Patients with mTBI and/or PTSD
- Brain Indices of Risk for PTSD after mTBI
- A Pilot Safety and Feasibility Study of High Dose Left Prefrontal Transcranial Magnetic Stimulation to Rapidly Stabilize Suicidal Patients with PTSD

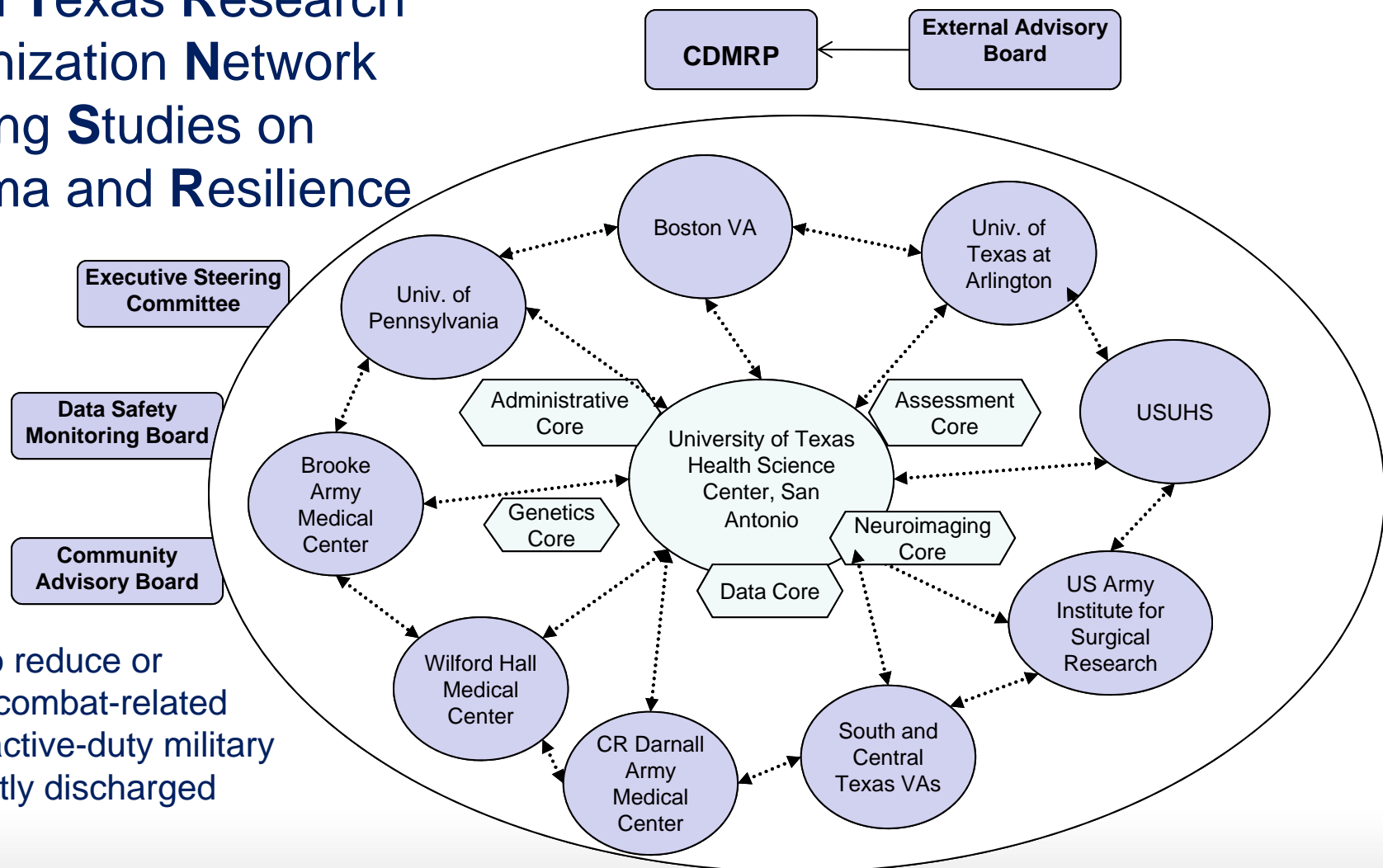
## Pilot Studies

- A Double-Blind, Placebo-Controlled, Flexible-Dose Pilot Clinical Trial of Once-Daily Extended-Release Tramadol for the Treatment of PTSD
- Novel Functional and Structural Biomarkers of Neuroinflammation and White Matter Change in TBI: A Potential New Diagnostic and Therapeutic Approach
- Improving Walking and Balance in Veterans with TBI
- Exercise: A Novel Treatment for Combat PTSD
- Cardiovascular Risk Markers in Veterans with PTSD
- The Use of Qualitative Methods to Support Clinical Trial Studies in PTSD-TBI Research
- Reliability and Initial Validation of the INTRuST Structured Clinical Interview for TBI in the Military Setting (SAFE-TBI)

# Collaborations: STRONG STAR



## South Texas Research Organization Network Guiding Studies on Trauma and Resilience



**Vision:** To reduce or eliminate combat-related PTSD in active-duty military and recently discharged veterans

# STRONG STAR Projects



- Outcomes of Prolonged Exposure and Cognitive Processing Therapy used in the Treatment of Combat Operational Stress Reactions in Deployed Settings
- Prolonged Exposure Treatment for PTSD Symptoms in Primary Care Settings
- Prolonged Exposure for PTSD among OIF/OEF Personnel: Massed vs. Spaced Trials
- Cognitive Processing Therapy for Combat-Related PTSD
- Individual PE vs. Couples' Cognitive-Behavioral Therapy for Combat-Related PTSD
- Treatment of Chronic Stress Reaction and Chronic Pain after Traumatic Orthopedic Injury: A Randomized Clinical Trial
- Prolonged Exposure Therapy for PTSD in Burn Patients
- Alcohol Use Disorder in PTSD Patients Treated with SSRI's: An Alcoholic Subtype Hypothesis of Vulnerability
- Prevalence of Fibromyalgia in PTSD Patients and Family Members
- The Impact of the Treatment of PTSD on Comorbid Insomnia and Pain
- Neuroimaging Studies of PTSD and PTSD Treatment among Combat Veterans
- Who gets better and why? Predicting Outcome Trajectories in STRONG STAR Trials
- Genetic and Environmental Predictors of Combat-Related PTSD
- Longitudinal Examination of Changes in Hypothalamic Pituitary Adrenal (HPA) Axis Responses to Stress in Military Subjects
- Mechanisms of Vulnerability to PTSD: The Role of Early Life Stressors

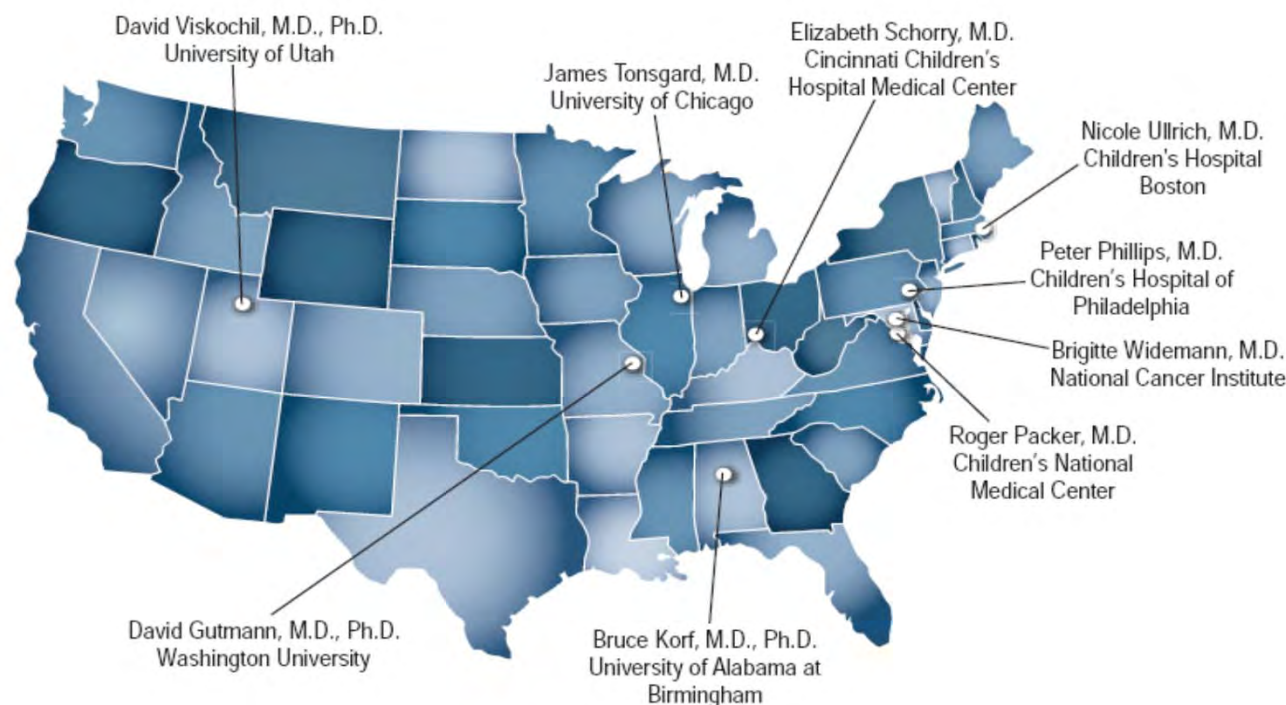
# Collaboration: Prostate Cancer Clinical Trials Consortium



**Goal:** Develop the infrastructure to increase patient accrual to Phase I/II clinical trials and expedite bringing better therapies to patients.

- 13 cooperating sites increase trial accessibility and rate of completion
- Have recruited more than 2,300 patients
- More than 10% of patients are from minority populations
- Have conducted 83 Phase I/II or Phase II studies
- Have investigated 50+ drugs
- Eight potential new therapies have moved into Phase III trials

# Collaborations & Partnerships: Neurofibromatosis Clinical Trials Consortium



- Phase II trial of Sirolimus (rapamycin) for the treatment of plexiform neurofibromas in patients with NF1
- Phase II study of lovastatin for the treatment of NF1-associated learning and memory impairments
- Phase II study of Everolimus (RAD001) for treatment of low grade gliomas

# Quality of Life

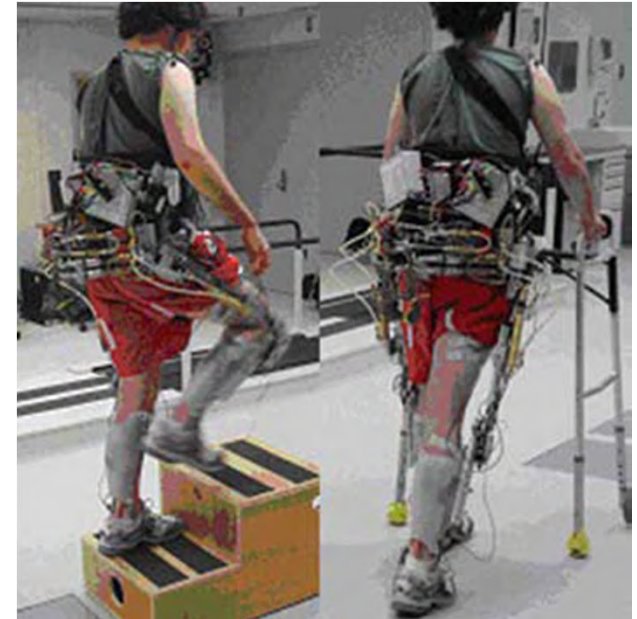


# Quality of Life: Hybrid Neuroprosthesis



## **FY04 PRMRP Investigator-Initiated Award Dr. Ronald Triolo, Case Western Reserve Prototype Hybrid Neuroprosthesis**

- Provide the means to stand, walk, climb steps and exercise
- Prevent or reverse deleterious effects of paralysis
- Prototype hybrid neuroprosthesis that enhances personal mobility for paraplegics:
  - Exoskeletal bracing
  - Implanted functional electrical stimulation
  - Braces lock and unlock joints so walking can be more fluid and natural
- Prototype pilot study:
  - Paraplegic and able-bodied volunteers
  - Paraplegic evaluation (one subject): exoskeletal bracing heavy, but provided functional support



# Quality of Life: Hybrid Neuroprosthesis

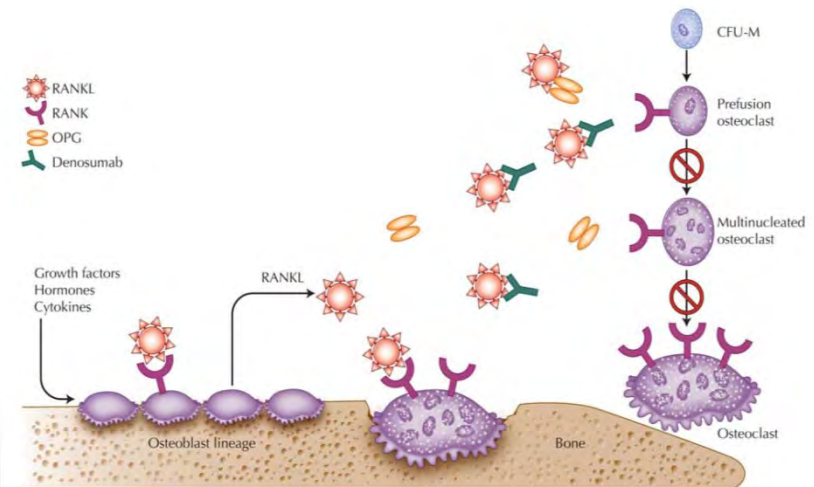


# Quality of Life: Denosumab



## FY02 PCRP Idea Development Award Dr. Evan Keller University of Michigan

- Preclinical studies funded by CDMRP found that blocking the activity of RANKL (receptor activator of NF $\kappa$ B ligand) is effective in diminishing progression of prostate cancer growth in bones
- These RANKL studies led to the development of denosumab, a monoclonal antibody against RANKL
- Denosumab is currently being studied in 26 Phase III clinical trials across a range of conditions including osteoporosis, cancer treatment-induced bone loss (e.g. hormone ablation), bone metastases, multiple myeloma and rheumatoid arthritis
- In November 2010, the FDA approved denosumab for treatment of bone loss during cancer treatment based on three independent studies that showed it was more effective than the standard of care
- XGEVA<sup>TM</sup> for cancer and Prolia<sup>TM</sup> for osteoporosis are now available to patients



# Quality of Life: Prazosin



**FY07 PH-TBI Research Program**

**Dr. Murray Raskind**

**Seattle Institute for Biomedical and Clinical Research**

**Got Nightmares?**

- In a small, open-label study, Prazosin appeared to reduce debilitating trauma nightmares in Service Members who had deployed to Iraq
- Military physicians have been prescribing Prazosin to soldiers in combat since 2005
- Approximately 26,000 Vietnam veterans are already taking Prazosin for chronic PTSD
- This study will develop an effective pharmacologic treatment to reduce the disabling morbidity of chronic PTSD in this new generation of combat veterans
- Study Trials have been conducted at the VA Puget Sound, Madigan Army Medical Center and Walter Reed Army Medical Center
- Ongoing recruitment at Madigan Army Medical Center

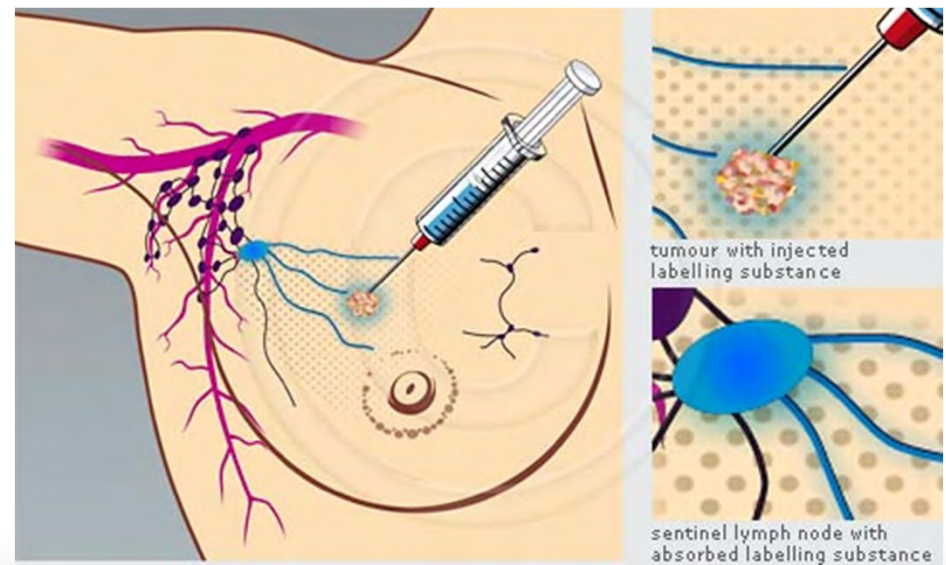
# Quality of Life: Sentinel Lymph Node Biopsy



**FY97 BCRP Career Development Award and FY99 BCRP Clinical Translational Research Award**

**Dr. Kathryn Verbanac  
East Carolina University**

- Supported a multi-center clinical trial testing the validity and accuracy of sentinel lymph node biopsy in predicting the spread of disease
- Accurately identifying the first nodes that receive lymph drainage allowed for a change in practice
- Results of the clinical trial contributed to what is now the current standard of care for breast cancer staging
- Also identified prognostic markers in sentinel node metastases by RT-PCR to improve accuracy of staging by pathology alone



# Innovators and Leaders



# Innovation: Sniffing Dogs



## FY06 OCRP Idea Development Award Dr. Touradi Solouki University of Maine

- Exhaled breath condensate (EBC) is used as a source of biomarkers that may distinguish women with ovarian cancer from healthy controls
- Trained dogs can “sniff out” ovarian cancer in EBC with 97% accuracy
- EBC is analyzed by Gas Chromatography Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (GC/FT-ICR MS) to identify biomarkers
- End result: a “breathprint”



Photos courtesy of Drs. Michael McCulloch and Touradj Solouki  
Heffner C, Silwal I, Peckham JM, Solouki T. 2007. *Environ Sci Technol* 41(15):5419-5425.

J. E. Szulejko, M. McCulloch, J. Jackson, D. McKee, J. Walker, T. Solouki, “Evidence for Cancer Biomarkers in Exhaled Breath – A Review”, *IEEE Sensors J*, 10 (1), 185-210, 2010

# Innovation: Sniffing Dogs



## A superb bioinformatic approach

- Uses excellent analytical capabilities to sift through myriad of signals for correct identification!
- Excellent brain power that exceeds current bioinformatic capabilities to filter noise and make sense of “real” data and hidden correlations!

## An incredible detection system

- Contains thousands of sensors
- 10,000 to 100,000-times more sensitive than humans
- Threshold sensitivity: one part per trillion (1ppt)
- Uses a large volume sample size
- Uses biological pre concentration approach
- Optimized and evolutionary molecular selectivity

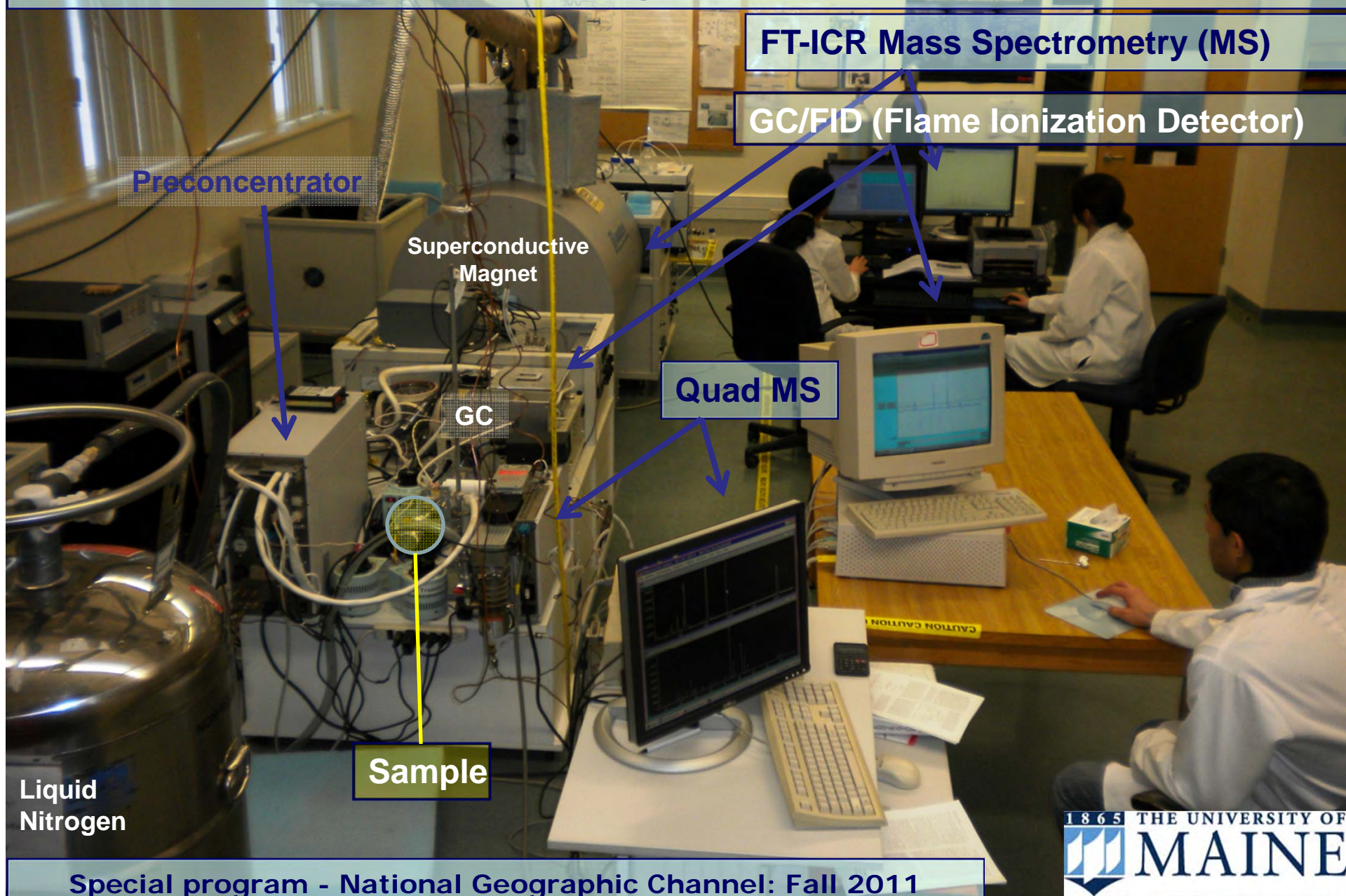
**Can we capture information as sensitive as a Dog's Nose? *Yes, with individual compounds!* The developed technology can be used to resolve complex mixtures containing thousands of chemicals!**



*Photos courtesy of Drs. Michael McCulloch and Touradj Solouki*

*D.B. Walker et al. / Applied Animal Behaviour Science 97 (2006) 241–254*

# A full room of equipment and personnel to approximate A Dog's Nose!



# Innovation: Sleep Management System



## FY99 PRMRP Investigator Initiated Award Dr. Gregory Belenky, WRAIR Wristwatch Actigraph

- Problem: Sleep loss (total sleep deprivation and sleep restriction for operational realities) impairs cognitive readiness
- Solution: Sleep as an item of re-supply
- Device measures how much sleep you have on hand and estimates current cognitive readiness



Warfighter at 100%  
Good to go  
for at least  
16 more hours



Warfighter at 60%  
Good to go  
for 12-16 more hours  
with countermeasure  
(e.g., caffeine)



Warfighter at 40%  
Good to go  
for 6 more hours  
with countermeasure  
(e.g., caffeine)



Warfighter at 0%  
Needs at least  
6 hours of sleep  
to return to duty



# Answer Current Needs



# Answer Current Needs: Early Detection of Ovarian Cancer



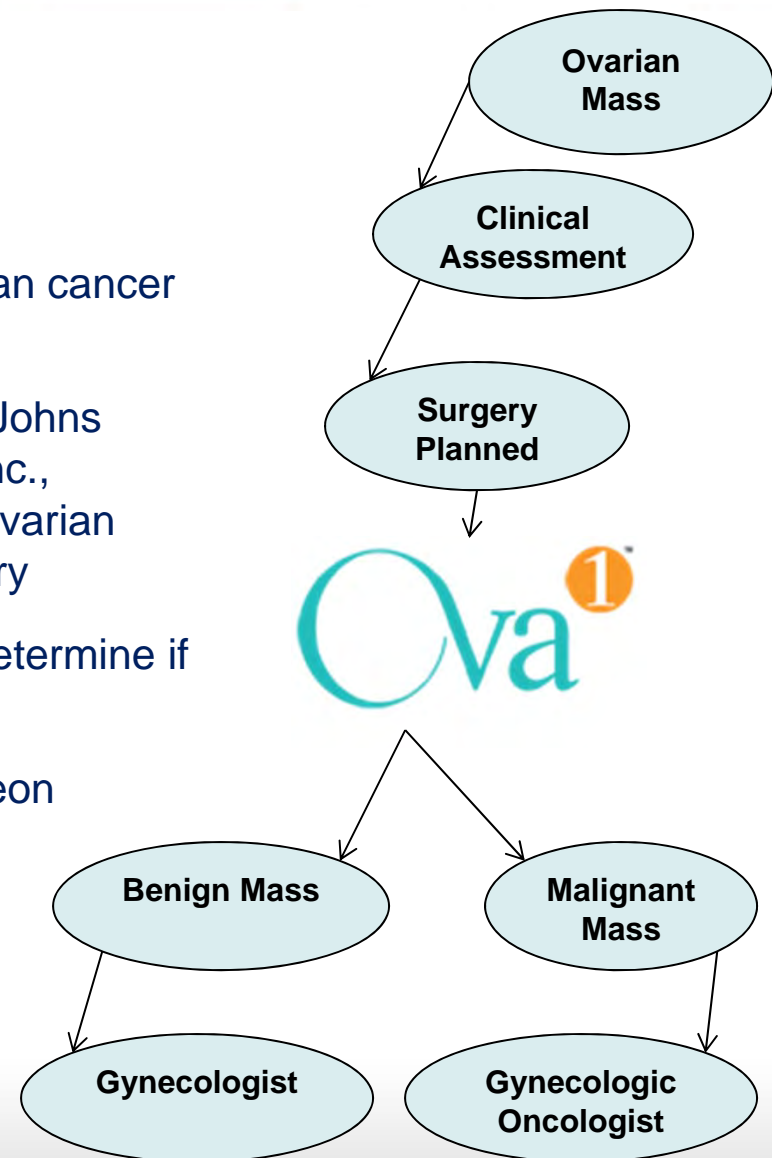
## FY03 OCRP Idea Development Award

Dr. Zhen Zhang

Johns Hopkins University

- Dr. Zhang discovered and validated a panel of ovarian cancer biomarkers for the early detection of ovarian cancer
- Based on his findings, Dr. Zhang and colleagues at Johns Hopkins University, in collaboration with Vermillion Inc., developed the OVA1 test to help physicians detect ovarian cancer in a woman with a pelvic mass prior to surgery
- OVA1 is the only FDA-approved blood test to help determine if an ovarian mass is malignant or benign
- OVA1 may help a doctor determine the type of surgeon to whom the patient should be referred
- In a double-blind clinical trial with dual assessment (pre-surgical assessment and OVA1), sensitivity for malignancy was 92%, compared to 72% without OVA1

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# Answer Current Needs: “Escape With Your Life”



## FY04 Institution-Based Research Program – Lung Cancer

Dr. Alexander V. Prokhorov, M.D., Ph.D.

M.D. Anderson Cancer Center



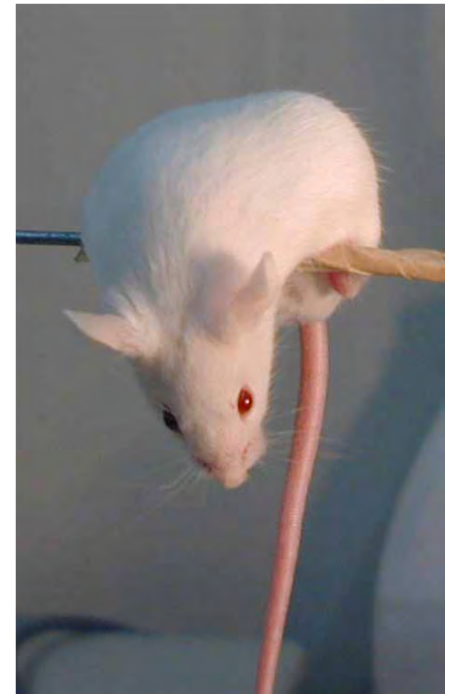
- Video game developed to educate teens on causes of lung cancer
- Encouraged stopping – or not starting – smoking
- More than 50% of study participants quit smoking at 6 months after playing the video game
- Awarded funding through Peer Reviewed Medical Research Program to modify game for use in military facilities

# Answer Current Needs: Neurofibromatosis Mouse Models



**FY01 NFRP Therapeutic Development Award**  
**Dr. Kevin Shannon**  
**University of California, San Francisco**

- Major effort to generate mouse models of NF1 and NF2
- These models did not exist prior to CDMRP grant funding
- NF Mouse Models Consortium generated accurate models many NF1- and NF2-associated tumors:
  - Plexiform Neurofibroma
  - Malignant Peripheral Nerve Sheath Tumor
  - Glioma
  - Meningioma
  - Myeloid Leukemia
- Mouse models have been provided to more than 50 laboratories worldwide



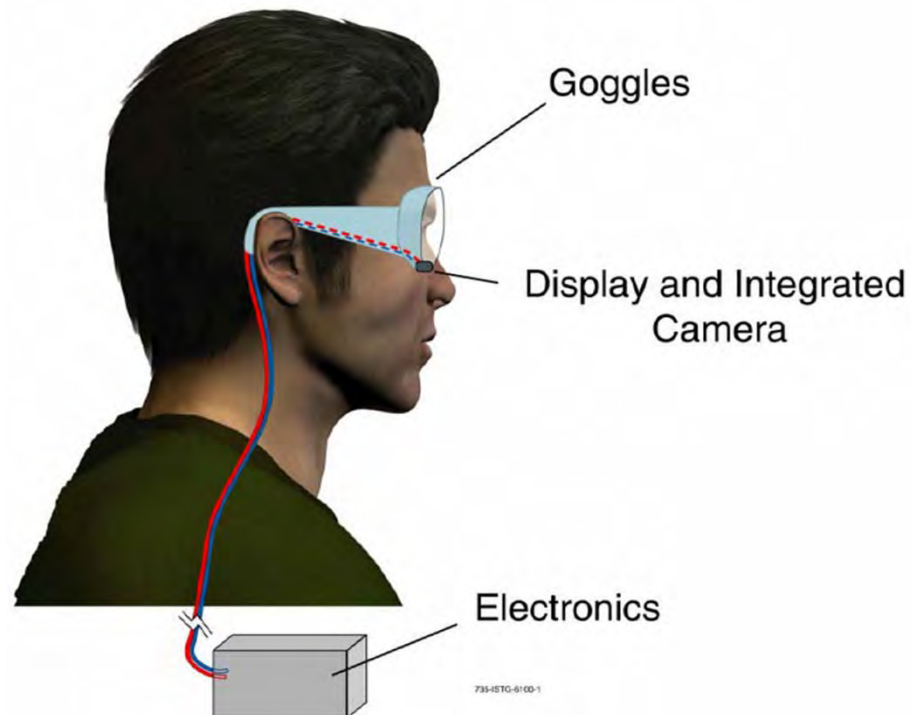
# Answer Current Needs: Early Diagnosis of mTBI



**FY07 TBI Advanced Technology-Therapeutic Development Award**

**Dr. Jamshid Ghajar, Brain Trauma Foundation, Inc.**

**Eye-Tracking Rapid Attention Computation**



- Mild TBI (mTBI) is difficult to diagnose
- EYE-TRAC will facilitate rapid diagnosis in theatre to identify Service Members with injury related complications that could have a negative impact on unit performance
- EYE-TRAC requires less than 30 seconds to measure
- Device accurately measures millisecond eye-target synchronization in predictable smooth pursuit eye movements
- Cohorts are fatigued soldiers, normal aging population, mTBI, ADHD, normal soldiers
- Software development underway to help distinguish between mTBI and PTSD



# Define and Reduce Health Disparities

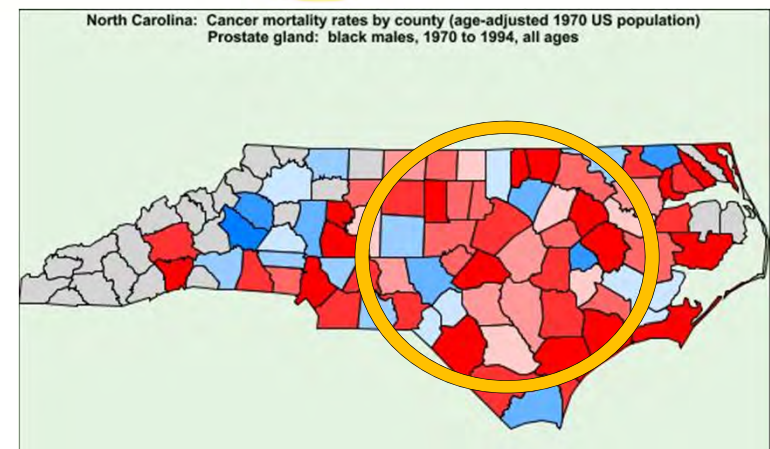
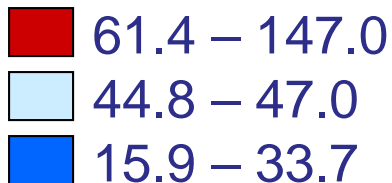
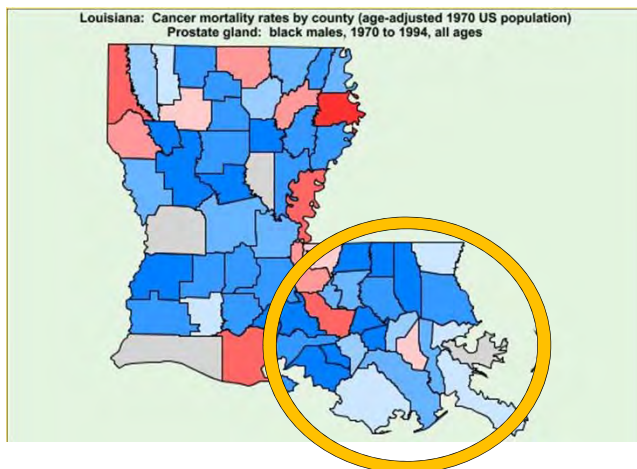
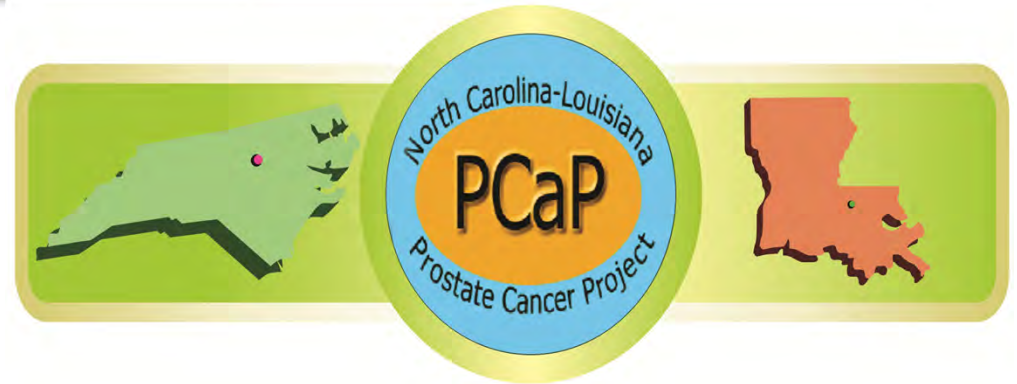


# Reduce Health Disparity: Prostate Cancer Project (PCaP) Consortium



**FY02 PCRCP Consortium Award**  
**James Mohler, M.D.**  
**Roswell Park Cancer Institute**

- In men under 65 years of age, the PCa mortality rate for African Americans (AA) is **3.1** times that of Caucasian Americans (CA)



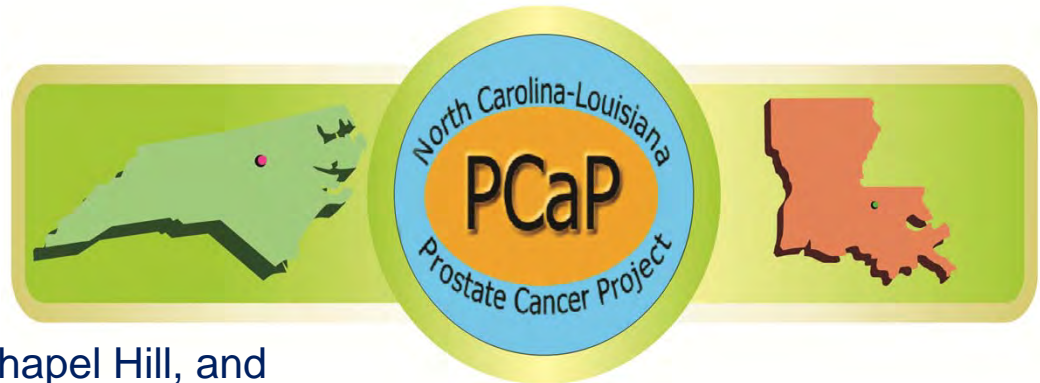
**Mortality / 100,000 Black Males 1970-1994**

US: 47.2 (46.9 – 47.5)  
LA: 42.2 (41.0 – 43.5)  
NC: 55.4 (54.0 – 56.8)

# Reduce Health Disparity: Prostate Cancer Project (PCaP) Consortium



**FY02 PCRP Consortium Award**  
**James Mohler, M.D.**  
**Roswell Park Cancer Institute**



- A consortium was developed by Roswell Park Cancer Institute, the University of North Carolina at Chapel Hill, and the Louisiana State University Health Science Center to study contributing factors to this health disparity, including:
  - limitations in access to health care due to socioeconomic status
  - treatment decision-making due to race- or culture-based factors
  - racial differences in tumor biology due to genetic or environmental factors (e.g. diet)
- More than 2,000 AA and CA men participated in the study
- AA men diagnosed with PCa tended to be younger, have less income and education, and have less effective interactions with health care providers than CA counterparts
- An unprecedented database of epidemiological data and biospecimens was generated for use by the wider PCa research community to answer disparity-related questions

# From our Consumer Advocates



“The whirlwind of CDMRP experience is challenging, enlightening, and inspiring from a personal and professional level. As a survivor, I am impressed with the researchers and love that they enjoy being able to meet people like me, patients who will be impacted the most by their efforts to eradicate cancer.”

“CDMRP is a vital link in the chain of events that will eventually bring relief to tens of thousands of American heroes. I am honored to be afforded the opportunity to play a role in that noble undertaking.”

“The people I have met and work alongside as a Consumer Reviewer for CDMRP are among the smartest and most compassionate medical professionals I have ever met. I am proud to be a small part of this truly incredible group that has the well-being of the many, for many generations to come, at heart.”

# CDMRP – Providing Hope



<http://cdmrp.army.mil/>

